**Authors' Response to:**

**Review of Paulozzi, LJ, et al, "Lack of Evidence that Prescription Drug Monitoring Programs Decrease Deaths from Opioid Overdose"**

**By Katherine Hempstead**

**Questions to address in the report:**

Are the study objectives clearly stated and appropriate? (Yes, No, Unsure) Why?

Yes.

**Is the overall study design appropriate for the study objectives? (Yes, No, Unsure) Why?**

1.  I don't believe so. First of all there is no theoretical model to really describe the mechanism through which  PDMPs are supposed to impact overdose and/or MME. This theoretical description should not treat the PDMP as a monolith, but should discuss particular features of PDMPs that are intended to have certain effects.  There seemed to be relatively little thought given to how PDMPs are supposed to work.

2.  The presence or absence of these features in state PDMPs should be included in the empirical analysis. Additionally, much more thought should be given to other determinants of MME and overdose – practice style, age structure, morbidity, access to health care/supply of health care providers , supply and  quality of street drugs – all of these things are important, but were really not at all developed in this study or included in the multivariate analysis.

3.  Also, rather than combine all of the drugs into one MME – the authors might have developed and tested theories about individual opiates.

*Response:*

*1.  We have elaborated on the introduction to point out that most overdose deaths are associated with abusing drugs and obtaining them without prescription, and PDMPs have been designed for and touted as a way to prevent drug diversion, ie, routing drugs to people for whom they weren't prescribed who will use them recreationally.*

*2.  Age was examined as a possible covariate, along with race, ethnicity, income, education, and urbanization, all variables that we thought a priori might have an impact on the outcomes of interest. It is not clear how we would quantify other variables such as practice style, morbidity, and street drug availability. Including yet other suggested variables in the analysis was possible but not necessarily indicated.  There was, for example, no previous literature to show that providers per capita are associated with overdose rates. (In any case, providers seems to be a more proximal exposure than the*

*bottom line, the grams per capita consumed by the population). With respect to PDMP-specific covariates, we do know the year each PDMP started, but there was no literature showing that PDMP longevity was associated with effectiveness. Basically we decided in advance to include those variables that were likely to have an impact, not all possible variables.*

*3. We did do a comparison of drug consumption data broken down by DEA Schedule because literature suggested PDMPs might effect Schedules differently. As a result, hydrocodone was singled out because it was the only Schedule III drug tracked by DEA. There may be state-specific practice variations in which opioids are favored, but that doesn't seem important if there doesn't appear to be any difference in the overall morphine milliequivalents per person of opioids combined. Using less of one opioid and more of another, especially if from the same Schedule, doesn't constitute a net impact of a PDMP.*

**Are the methods and analysis plan appropriate for the study objectives? (Yes, No, Unsure) Why?**

1. No I don't believe so. The analysis should have been a "difference in differences" approach, with the inclusion of years from PDMP states before the PDMP was developed. From the discussion in the paper it appeared that states were treated as PDMP states for the entire period, no matter when their PDMP went into place. If this was not the case it was pretty much impossible to tell that from the paper.

2. As mentioned above I think there should have been models for individual drugs, rather than just MME and opiate mortality.

3. I think the control variables used were inadequate. Also, there are practically no tables in the paper that show the results. The one table doesn't show any of the covariates other than year and the dummy variables for D.C., which are of little interest. Frankly I think they could have just taken the D.C. data out of their analysis if it was unreliable. The authors state that MME was a RH side variable for the mortality regression, but that coefficient is not shown in the table, nor is the result for that coefficient described in the text.

4. The graphs are not appropriate and are very much over-used. One or two graphs would have been more than enough, but the paper lacks basic information that should be in tables. For example, there should have been a table that showed for each state with a PDMP, when it came into existence and what its features were.

5. I also think they could have considered or at least discussed the possibility of estimating this at the sub-state level. The ARCOS stuff is published at the three digit zip code level.

*Response:*

*1. The regression analysis was in fact a "differenced" analysis. The text at the top of page 9 says this:*

Because of the high level of temporal autocorrelation present in the dependent variables, we had to transform these variables by first-order differencing. Differenced rates represent the year-to-year increase (or, if negative, the decrease) in the variable's value. MME rates were similarly modeled as a function of the presence of a PDMP and the same covariates (but not as a function of the mortality variables).

*In other words, year-to-year differences in the outcomes were evaluated as a function of presence or absence of a program.*

*It was not possible to evaluate the difference resulting from the startup of a new PDMP because only a few states actually "developed" a PDMP during this time period. See the text added to page 14:*

Unfortunately, an alternative design that evaluates changes in state indicators before and after the establishment of PDMPs to control for factors that may have led to PDMP legislation was not possible with available data. Information on opioid-related mortality is only available after 1999. Drug distribution data is only available after 1997. Only a few states started PDMP data collection after 1999 and prior to 2005 thus allowing sufficient observation periods pre and post PDMP implementation. Such a study should be possible in a few years.

*But, to assure ourselves we were not missing any "difference of differences" because of the inclusion of so many states that either had or did not have a program during all seven study years, we did a focused analysis of the six states that contributed "state-years" to the analysis both before and after implementing a program. We found no evidence of a statistically significant "difference of differences" in the death rate (by either definition) before and after implementing their PDMPs. Moreover, opioid drug sales did not differ before and after program implementation in those states. See the appendix to this document for the details of this analysis.*

*States were not treated as PDMP states for the entire period. Their PDMP status was evaluated each year. We modified the sentence that said this as follows:*

For each of the seven study years and 51 states, a total of 357 state-years of observation, we determined the presence or absence of an operational PDMP

*2. We responded above to the suggestions to model individual drugs.*

*3. Control variables were discussed in the response above. The covariates were added one by one looking for any resulting significant protective effect of PDMPs. But no such variables were found, so we showed the covariates for the final model without them. The DC data was an outlier. We discussed excluding it but decided in the end to keep it in. The morphine milliequivalent variable (MME) was not significant in the final model and therefore was not included in the Table.*

*4. We believe that each of the six figures makes a separate, important point and none are redundant. As noted above, we did not include other characteristics of PDMPs in the analysis and therefore don't agree that those characteristics should be tabulated. We believe the figures give a much better picture of the situation than tables of annual rates*

*would, and we believe the table of multivariate results adequately supports the conclusions the reader might draw from the figures of unadjusted data. We have, however, added a table showing the rates for the outcomes by different categories of states for the entire time period (new Table 1).*

*5. Yes, ARCOS data is available at the 3-digit zip code level by drug by year. And yes it might have been possible to see whether the presence of a PDMP affected drug consumption in the poorest or most urban zip areas more or less. (Mortality data is not available by zip code nationally.)  However, we already know that drugs distributed in one state may be consumed by residents in another, as noted on page 14.  This is even more true when talking about adjacent zip codes within a state. The resulting exposure misclassification would bias any comparisons toward finding no difference. And again, the bottom line appears to be that PDMPs do not even come close to affecting total consumption.  It may be interesting to see if they lower it in one zip and raise it in another, but this doesn't change the overall conclusion.*

**Were the data analyzed in such a way to address the objectives of the study appropriately? (Yes, No, Unsure) Why?**

In my opinion, no. See above.

**Are the study results presented and interpreted appropriately and completely? (Yes, No, Unsure) Why?**

See above.

**Are the study conclusions, policy implications, and recommendations appropriate and complete? (Yes, No, Unsure) Why?**

See above.

**Are there any other comments on the report?**

I think this is a missed opportunity. The subject is extremely important and of great interest to many people.

*Response:*

*We believe that this is the best approach with the data available and that the findings will prompt useful discussion about the impact of such programs.  We welcome any follow-up observations.*

*Appendix*


OCTOBER 13, 2009 (rev. October 20)
NOTE TO "STUDY A" TEAM / FOR THE RECORD
FROM ED KILBOURNE


RE: "DIFFERENCE OF DIFFERENCES" ANALYSIS

**SUMMARY**
I've now completed a focused and much more extensive "Difference of Differences" analysis on the "Study A" data. The results show <u>no</u> statistically significant[1] differences of differences for any of the outcomes.


**RATIONALE**
The reason for investigating this matter in further depth is the possibility that our regression analysis of differenced values could have "diluted" an effect that would be more clearly visible in a study limited to the states that changed status (from non-PDMP to PDMP) during the study period. (There were no states changing from PDMP to non-PDMP status.)


**INTRODUCTION**
There were six states that contributed both PDMP and non-PDMP state-years to the study. They (and their PDMP starting years) are shown in Table 1.

Table 1.

| STATE | START |
|-------|-------|
| PA | 2002 |
| VA | 2003 |
| ME | 2004 |
| WY | 2004 |
| MS | 2005 |
| NM | 2005 |

For the descriptive data that follow, I normalized the years of program start by subtracting the study starting year less one from each of the program years for each state. Thus Year=1 for PA represents 2002, but Year=1 for WY indicates 2004 (i.e., events occurring two years later). Year=0 means the year prior to implementation, Year= -1 means two years prior to implementation, Year= -2 means three years prior, and so forth.


**DRUG OVERDOSE MORTALITY**
The rates of drug overdose mortality (deaths per 100,000 persons) for the six states are shown in Table 2.

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[1] Differences discussed herein are considered statistically significant where P ≤ 0.05.
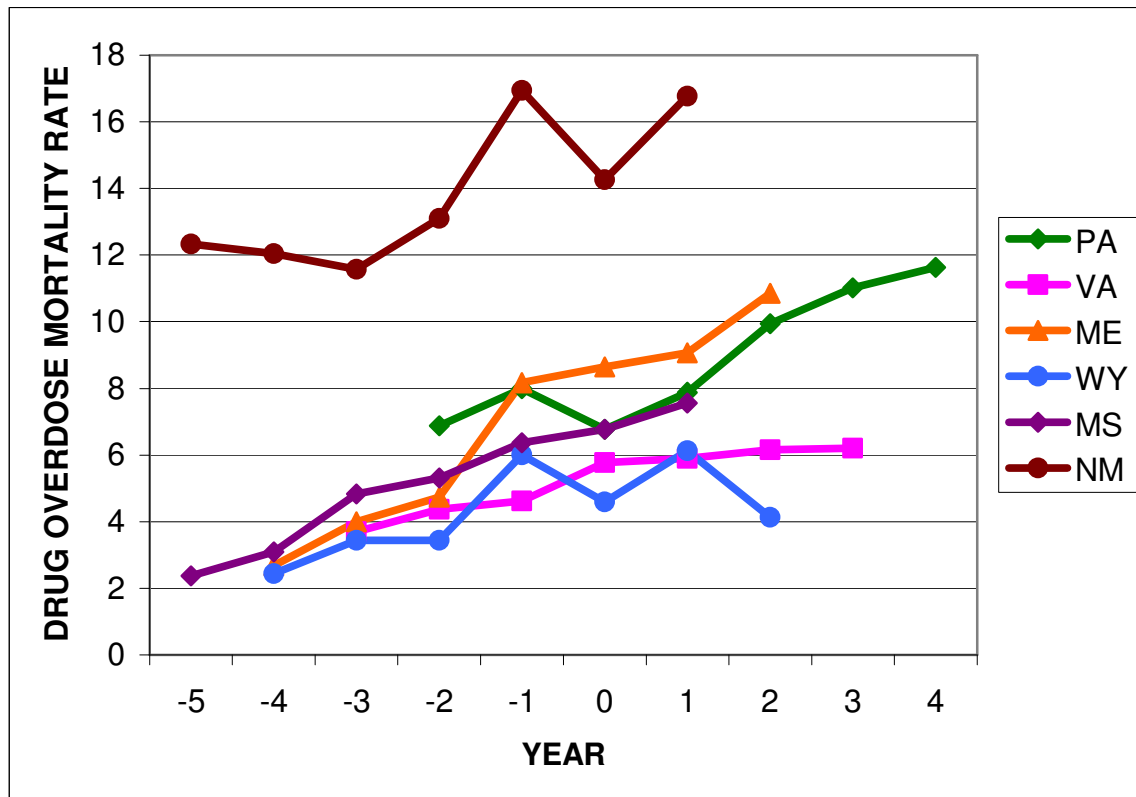
Table 2.

| YEAR | PA | VA | ME | WY | MS | NM |
|------|------|------|-------|------|------|-------|
| -5 | | | | | 2.37 | 12.33 |
| -4 | | | 2.68 | 2.44 | 3.09 | 12.04 |
| -3 | | 3.70 | 4.00 | 3.44 | 4.83 | 11.57 |
| -2 | 6.88 | 4.37 | 4.74 | 3.44 | 5.31 | 13.10 |
| -1 | 8.00 | 4.62 | 8.17 | 6.01 | 6.37 | 16.94 |
| 0 | 6.78 | 5.78 | 8.64 | 4.59 | 6.78 | 14.26 |
| 1 | 7.88 | 5.90 | 9.06 | 6.13 | 7.56 | 16.77 |
| 2 | 9.94 | 6.16 | 10.85 | 4.13 | | |
| 3 | 11.01 | 6.21 | | | | |
| 4 | 11.63 | | | | | |

☐ = No PDMP

☐ = PDMP

If one graphs these rates for the six states over time, they appear as shown in Figure 1.

Figure 1.



The rates of drug overdose mortality in Table 2 and Figure 1 are in no way differenced. Note that they have a clear-cut upward trend.

Differenced values reflect the difference in a rate from the previous time period. A first-order year-to-year difference in a statistic is the statistic for one year after subtracting that same statistic for the previous year.

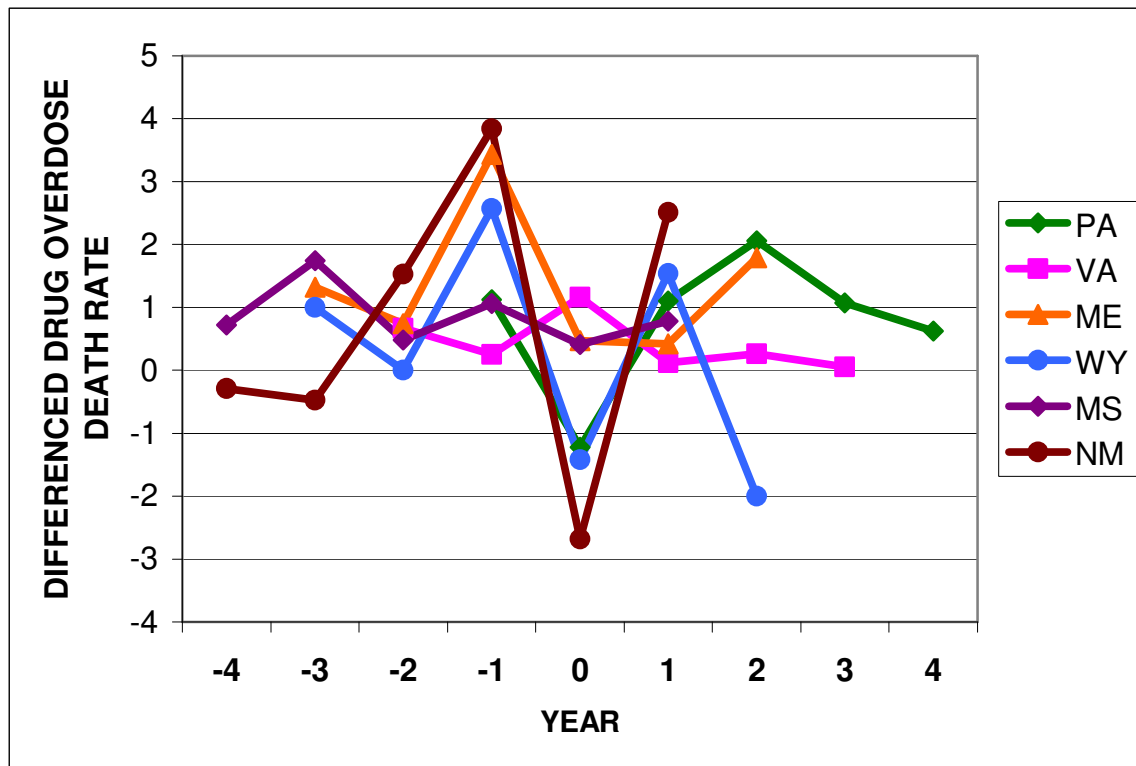The first-order differences for the above rates appear as follows in Table 3.

Table 3.

| YEAR | PA | VA | ME | WY | MS | NM |
|------|------|------|------|------|------|------|
| -4 | | | | | 0.72 | -0.29 |
| -3 | | | 1.32 | 1.00 | 1.74 | -0.47 |
| -2 | | 0.67 | 0.74 | 0.00 | 0.48 | 1.53 |
| -1 | 1.12 | 0.25 | 3.43 | 2.57 | 1.06 | 3.84 |
| 0 | -1.22 | 1.16 | 0.47 | -1.42 | 0.41 | -2.68 |
| 1 | 1.10 | 0.12 | 0.42 | 1.54 | 0.78 | 2.51 |
| 2 | 2.06 | 0.26 | 1.79 | -2.00 | | |
| 3 | 1.07 | 0.05 | | | | |
| 4 | 0.62 | | | | | |

= No PDMP

= PDMP

A line graph of these values over time is shown as Figure 2.

Figure 2.



Differencing is analogous to taking the first derivative in the Calculus. Thus, the pronounced upward trend (analogous to a sloped straight line) is mitigated (analogous to conversion of a straight, sloped line to a horizontal line by taking the first derivative). The question remaining now is whether the year to year differences are lower when YEAR $\geq 1$.

But before we can pool data points, one problem remains. Even after differencing, the statistics from the six states are by no means the same with regard to their means and variances. Between-state differences in their mean values could possibly decrease the sensitivity of the difference of differences analysis by amplifying the variance of data points in the two groups: "before" and "after" the intervention (the PDMP).

Between-state differences in variance are also potentially problematic. States with larger variances will tend to have "influential points" (much higher and much lower) after differencing and may have a disproportionate effect on any summary measures, potentially biasing the analysis in unpredictable ways. As an example, from observation of the above graph, one notes that the variance (over time) of the differenced rates from New Mexico seems to be substantially greater than that of most of the other states.

To deal with these problems, one convert the data into "standard scores" to equalize means and standard deviations. Note that making the overall means for the states equal will tend to amplify (not mask) a difference between "before" and "after." Standardizing the means does this by eliminating between state differences that are irrelevant to the "before" and "after" conditions.

Conversion of data to "Z-scores" normalizes both mean and variance. A Z-scored variable has a mean of zero and a standard deviation of one. The formula for standardizing data in this way is given as Equation 1.
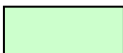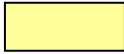
Equation 1.

$$Z = \frac{x - \mu}{\sigma}$$

where x is the value for a particular state and year, μ is the mean for the state, and σ is the standard deviation for the state. (There are nuances of standardized scoring that depend on whether one is dealing with population statistics or population estimates, but I omit them here for simplicity.) The standardized, differenced data for the drug overdose death outcome are shown in Table 4.

Table 4.

| YEAR | PA | VA | ME | WY | MS | NM |
|------|------|------|------|------|------|------|
| -4 | | | | | -0.33 | -0.48 |
| -3 | | | -0.04 | 0.45 | 1.97 | -0.56 |
| -2 | | 0.65 | -0.60 | -0.18 | -0.87 | 0.37 |
| -1 | 0.33 | -0.44 | 1.98 | 1.42 | 0.44 | 1.45 |
| 0 | -2.02 | 1.92 | -0.85 | -1.06 | -1.02 | -1.59 |
| 1 | 0.31 | -0.77 | -0.90 | 0.78 | -0.19 | 0.83 |
| 2 | 1.27 | -0.41 | 0.41 | -1.42 | | |
| 3 | 0.28 | -0.96 | | | | |
| 4 | -0.17 | | | | | |

□ = No PDMP

□ = PDMP

The same numbers, displayed graphically are shown in Figure 3:
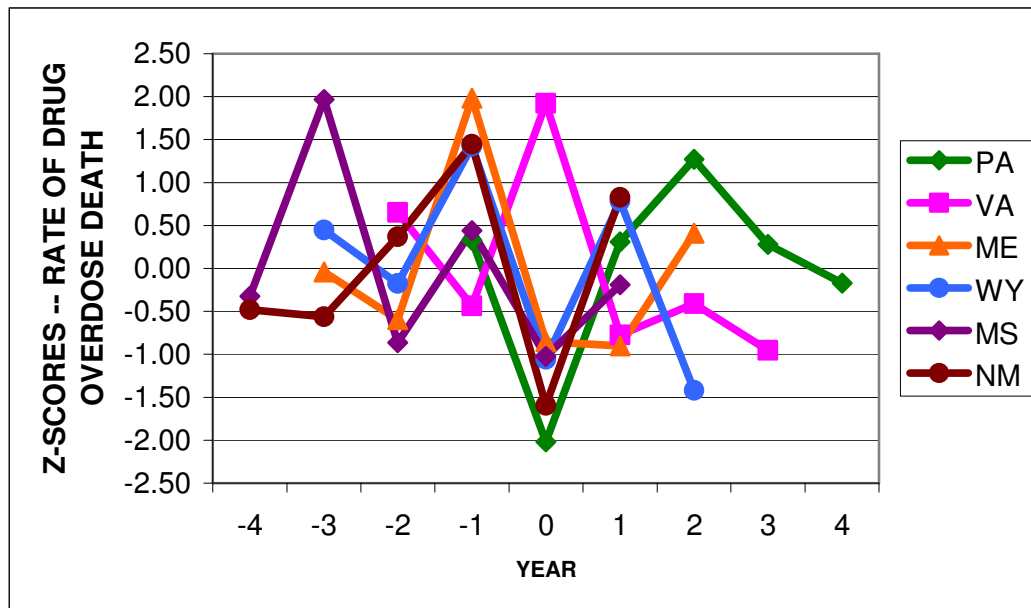


No particular difference is evident in Figure 3 at Year $\geq 1$. However, for further assurance, we divide the data points (now differenced and standardized) into two groups: "Before" and "After." The statistics derived are as follows:

Table 5.

| GROUP | N | MEAN | S.E. | DF | T | P |
|--------|-----|-------|------|-----|--------|--------|
| BEFORE | 23 | 0.04 | 0.24 | 34 | 0.3175 | 0.7528 |
| AFTER | 13 | -0.07 | 0.22 | | | |

There is a trend toward lesser year-to-year increases in drug overdose death rates in these 6 states. However, it is not nearly statistically significant at the 0.05 level.
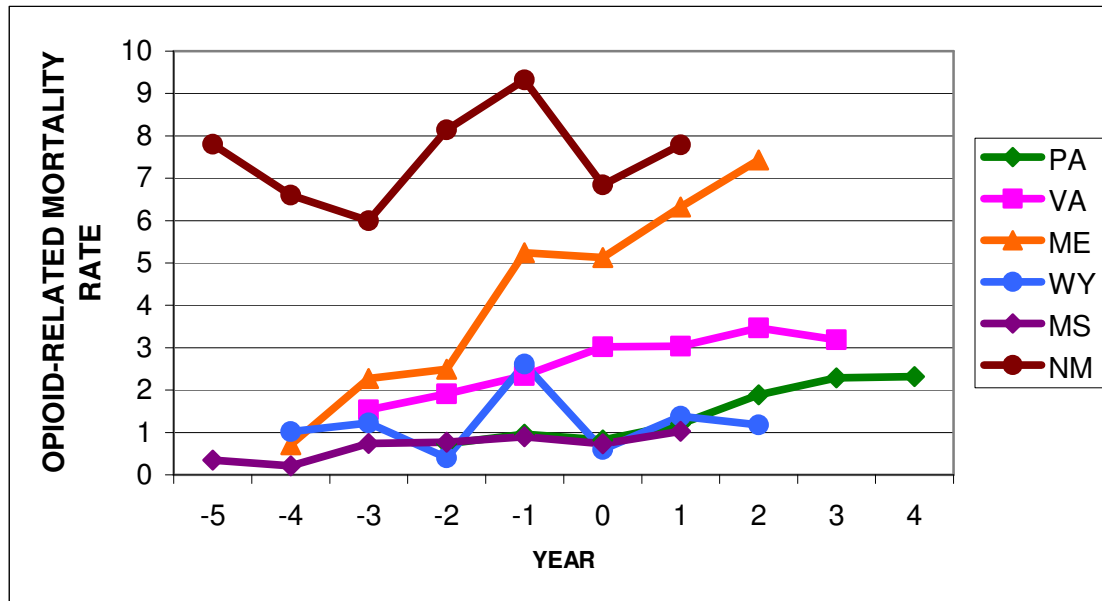
## OPIOID-RELATED MORTALITY
The parallel analyses for opioid-related mortality can be summarized in the following tables and figures:

Table 6.  Rate of opioid-related mortality by year relative to the starting year of the PDMP Program

| YEAR | PA | VA | ME | WY | MS | NM |
|---|---|---|---|---|---|---|
| -5 |  |  |  |  | 0.35 | 7.80 |
| -4 |  |  | 0.71 | 1.02 | 0.21 | 6.60 |
| -3 |  | 1.53 | 2.27 | 1.22 | 0.74 | 6.00 |
| -2 | 0.73 | 1.91 | 2.49 | 0.40 | 0.77 | 8.14 |
| -1 | 0.96 | 2.34 | 5.24 | 2.61 | 0.90 | 9.32 |
| 0 | 0.82 | 3.02 | 5.13 | 0.60 | 0.73 | 6.84 |
| 1 | 1.20 | 3.04 | 6.32 | 1.38 | 1.03 | 7.79 |
| 2 | 1.89 | 3.47 | 7.43 | 1.18 |  |  |
| 3 | 2.29 | 3.19 |  |  |  |  |
| 4 | 2.32 |  |  |  |  |  |

= No PDMP

= PDMP

Figure 4. Opioid-Related Mortality Rates by Year Relative to the Starting Year of the PDMP Program
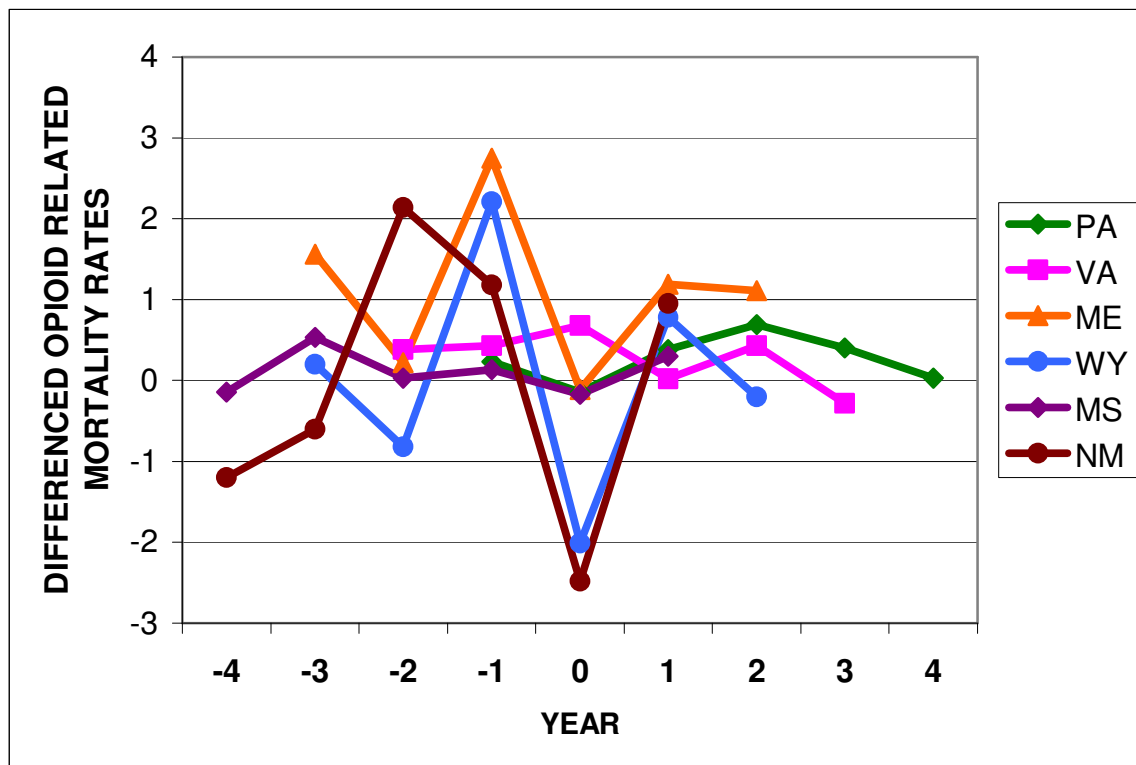


Differenced values of opioid-related mortality rates by state are as follows in Table 7 and Figure 5:

Table 7.

| YEAR | PA | VA | ME | WY | MS | NM |
|------|------|------|------|------|------|------|
| -4 | | | | | -0.14 | -1.20 |
| -3 | | | 1.56 | 0.20 | 0.53 | -0.60 |
| -2 | | 0.38 | 0.22 | -0.82 | 0.03 | 2.14 |
| -1 | 0.23 | 0.43 | 2.75 | 2.21 | 0.13 | 1.18 |
| 0 | -0.14 | 0.68 | -0.11 | -2.01 | -0.17 | -2.48 |
| 1 | 0.38 | 0.02 | 1.19 | 0.78 | 0.30 | 0.95 |
| 2 | 0.69 | 0.43 | 1.11 | -0.20 | | |
| 3 | 0.40 | -0.28 | | | | |
| 4 | 0.03 | | | | | |

$\square$ = No PDMP

$\square$ = PDMP

Figure 5.



The differenced rates of opioid-related mortality must be standardized, just as for the differenced drug overdose mortality rates:
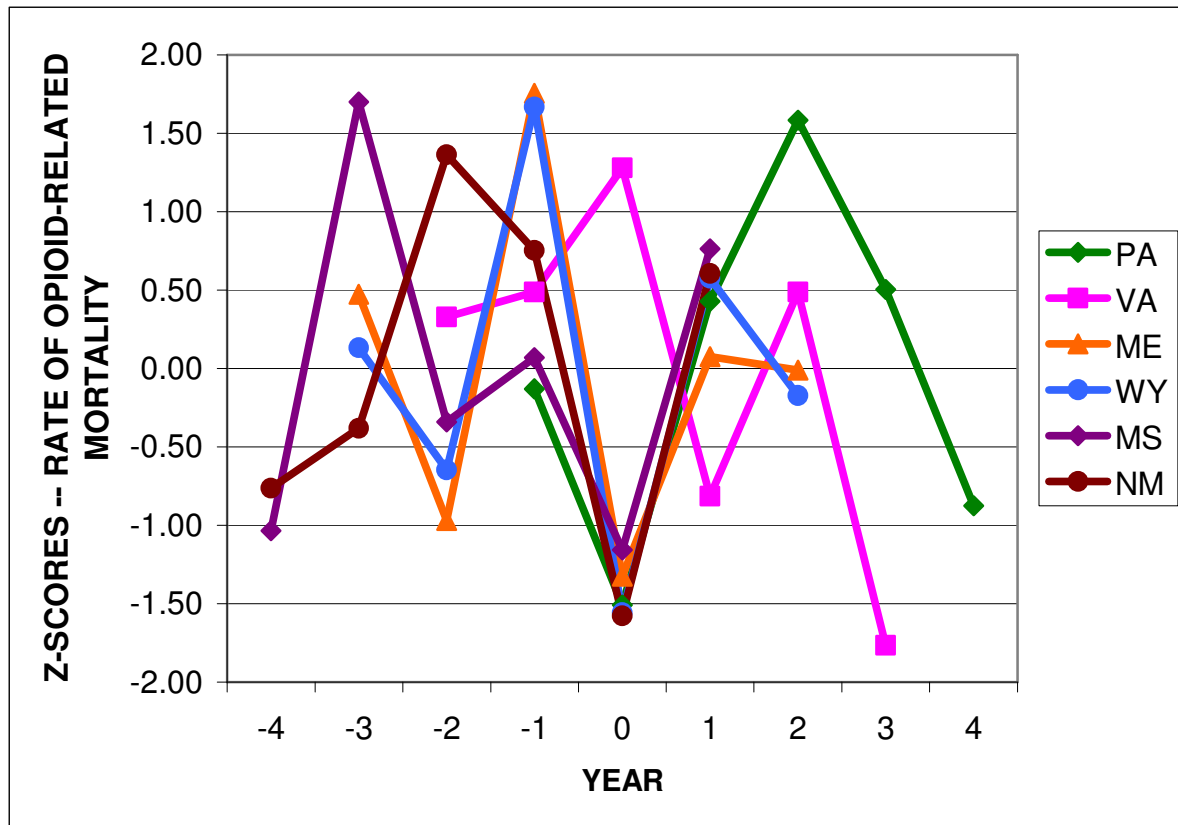
Table 8. Standard (Z) scores for opioid-related mortality rates.

| YEAR | PA | VA | ME | WY | MS | NM |
|------|------|------|------|------|------|------|
| -4 | | | | | -1.03 | -0.76 |
| -3 | | | 0.47 | 0.13 | 1.70 | -0.38 |
| -2 | | 0.33 | -0.97 | -0.65 | -0.34 | 1.36 |
| -1 | -0.13 | 0.49 | 1.75 | 1.67 | 0.07 | 0.75 |
| 0 | -1.51 | 1.28 | -1.32 | -1.56 | -1.16 | -1.58 |
| 1 | 0.43 | -0.81 | 0.08 | 0.58 | 0.76 | 0.61 |
| 2 | 1.58 | 0.49 | -0.01 | -0.17 | | |

$\square$ = No PDMP

$\square$ = PDMP

| | | | | | | |
|---|---|---|---|---|---|---|
| 3 | 0.50 | -1.77 | | | | |
| 4 | -0.88 | | | | | |

Figure 6. Standard (Z) scores for opioid-related mortality rates.



"Before and after" statistics for opioid drug overdoses can be calculated as before. They are shown in Table 9. As was the case for drug overdose mortality, there is no significant difference in opioid related mortality before and after implementing the PDMP. However, the opioid-related mortality analysis is slightly different in that the trend is toward a slightly worse outcome (that is, a greater year-to-year increase in rates of opioid-related mortality following institution of a PDMP.

Table 9.

| GROUP | N | MEAN | S.E. | DF | T | P |
|---|---|---|---|---|---|---|
| BEFORE | 23 | -0.06 | 0.23 | 34 | -0.4666 | 0.6438 |
| AFTER | 13 | 0.11 | 0.24 | | | |

## TOTAL MORPHINE EQUIVALENTS PER PERSON-YEAR (TOTALMEQ)
Finally, The parallel analysis for the third and final outcome variable, the total morphine milligram equivalents per person per year (TOTALMEQ), can be summarized in the following tables and figures:

13

Table 10. Undifferenced values of TOTALMEQ by state and year relative to PDMP start date.

| YEAR | PA | VA | ME | WY | MS | NM |
|------|-----|-----|-----|-----|-----|-----|
| -5 | | | | | 124 | 148 |
| -4 | | | 223 | 136 | 169 | 194 |
| -3 | | 166 | 306 | 166 | 208 | 246 |
| -2 | 199 | 219 | 389 | 222 | 264 | 287 |
| -1 | 246 | 265 | 477 | 291 | 331 | 339 |
| 0 | 292 | 314 | 550 | 376 | 370 | 389 |
| 1 | 351 | 376 | 672 | 429 | 406 | 413 |
| 2 | 451 | 406 | 720 | 468 | | |
| 3 | 487 | 417 | | | | |
| 4 | 536 | | | | | |

= No PDMP

= PDMP

Figure 7. Undifferenced values for TOTALMEQ
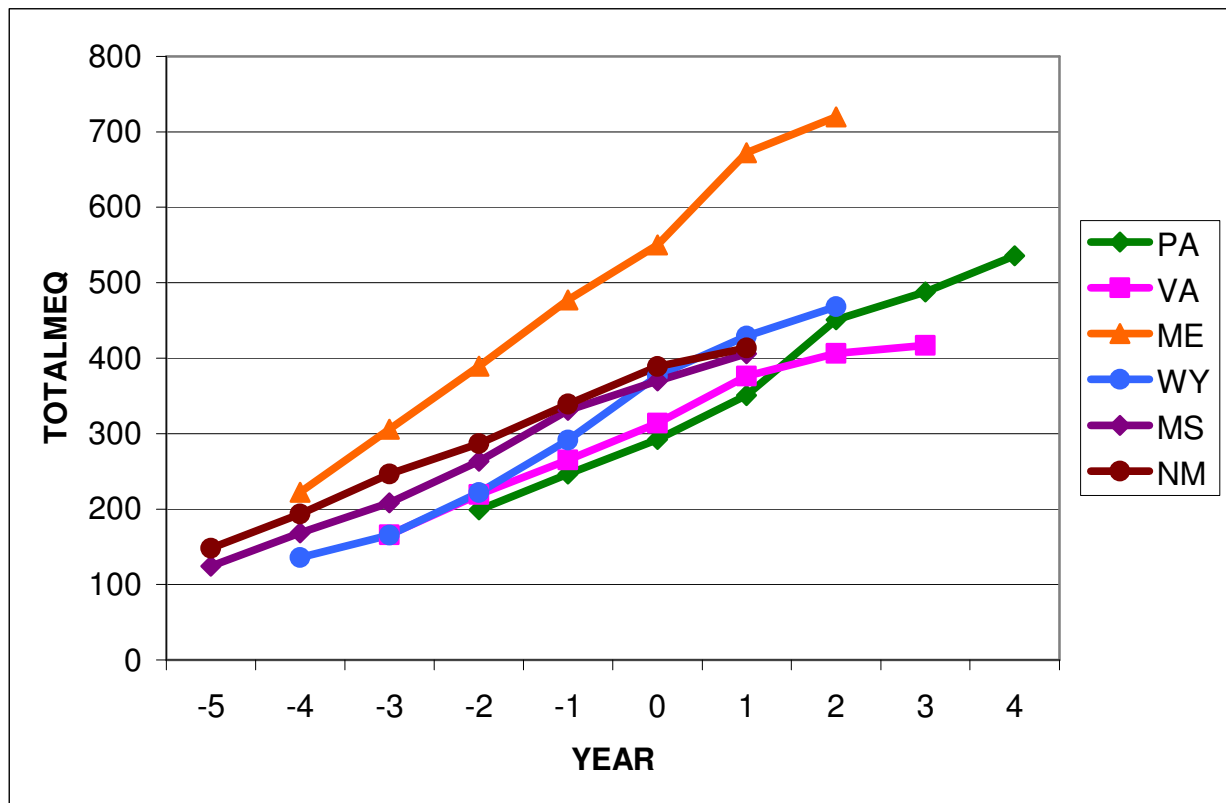
Table 11.  Differenced values of TOTALMEQ by state and year relative to PDMP start date.

| YEAR | PA | VA | ME | WY | MS | NM |
|------|-----|-----|-----|-----|-----|-----|
| -4 | | | | | 44 | 45 |
| -3 | | | 84 | 30 | 40 | 53 |
| -2 | | 53 | 83 | 56 | 55 | 41 |
| -1 | 47 | 46 | 88 | 69 | 68 | 52 |
| 0 | 46 | 49 | 73 | 85 | 39 | 50 |
| 1 | 58 | 62 | 123 | 53 | 36 | 24 |
| 2 | 100 | 30 | 48 | 39 | | |
| 3 | 37 | 11 | | | | |
| 4 | 48 | | | | | |

= No PDMP  
= PDMP

Figure 8.  Difference values of TOTALMEQ
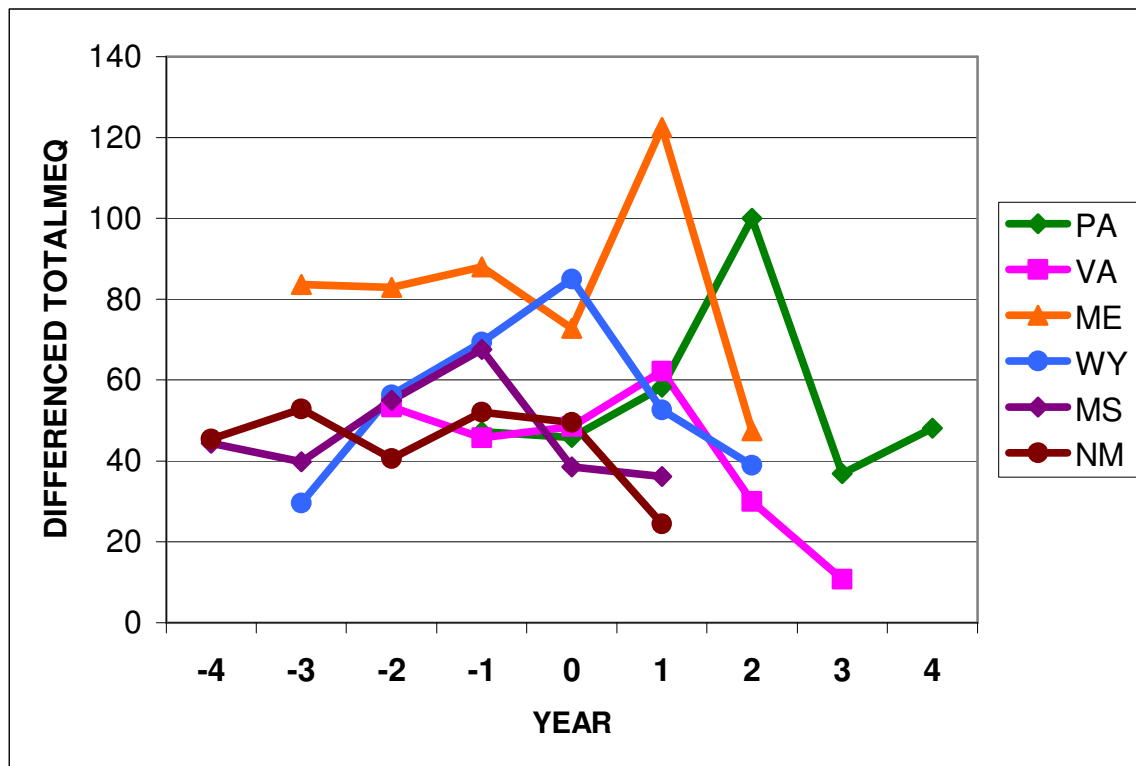


Table 12. Z-scored values of TOTALMEQ

| YEAR | PA | VA | ME | WY | MS | NM |
|------|-----|-----|-----|-----|-----|-----|
| -4 | | | | | -0.23 | 0.13 |
| -3 | | | 0.03 | -1.40 | -0.65 | 0.89 |
| -2 | | 0.69 | 0.00 | 0.06 | 0.73 | -0.36 |
| -1 | -0.43 | 0.24 | 0.23 | 0.77 | 1.87 | 0.81 |
| 0 | -0.50 | 0.40 | -0.45 | 1.62 | -0.76 | 0.55 |
| 1 | 0.11 | 1.20 | 1.79 | -0.15 | -0.97 | -2.02 |
| 2 | 2.13 | -0.69 | -1.60 | -0.89 | | |
| 3 | -0.93 | -1.84 | | | | |
| 4 | -0.38 | | | | | |

= No PDMP  
= PDMP

Figure 9. Z-scored values of TOTALMEQ
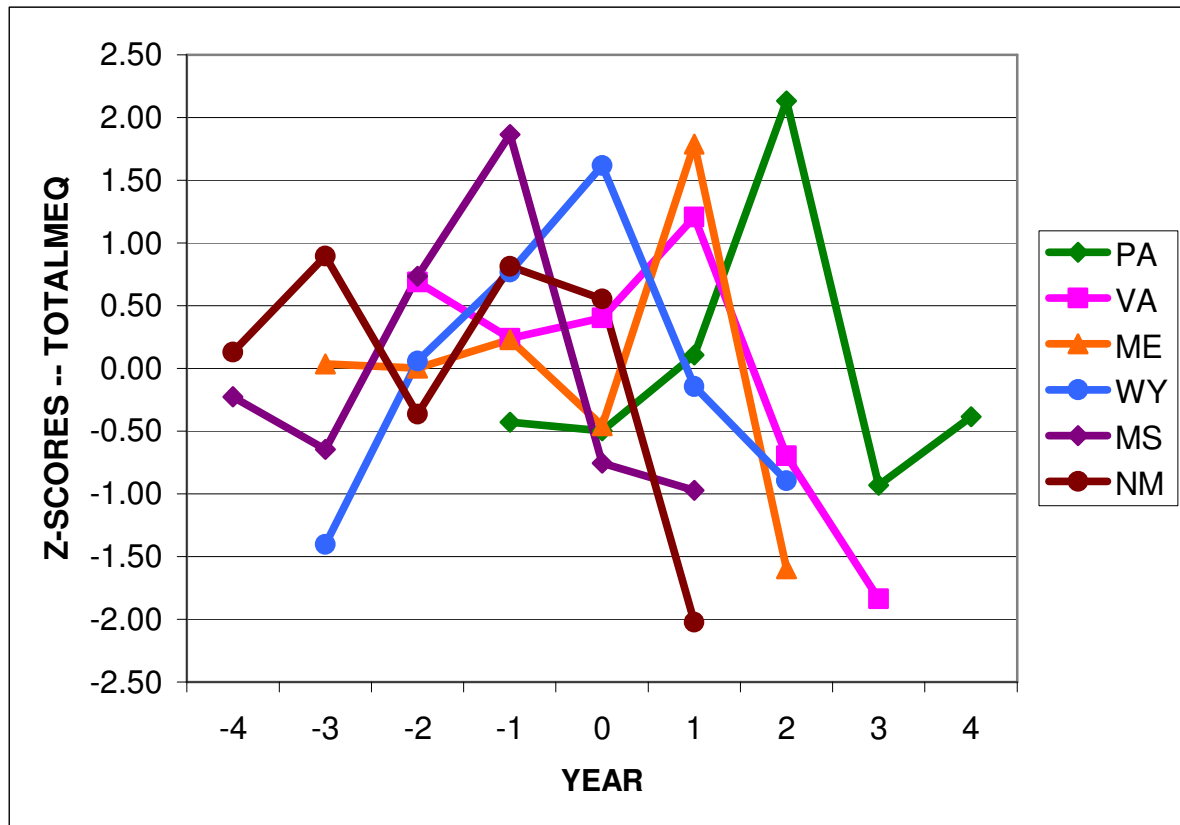


Table 13. "Before and after" comparison of TOTALMEQ

| GROUP | N | MEAN | S.E. | DF | T | P |
|--------|-----|-------|------|------|-------|--------|
| BEFORE | 23 | 0.18 | 0.16 | 16.6 | 1.275 | 0.2199 |
| AFTER | 13 | -0.33 | 0.37 | | | |

Thus the analysis of TOTALMEQ shows a trend toward lower year-to-year increases in total morphine equivalents per person in years occurring after institution of a PDMP. However, this trend is NOT statistically significant at the 0.05 level.

**CONCLUSION**

An analysis focused on the states that instituted PDMP's during the study period shows no statistically significant evidence of an impact of the programs on death rates (using either definition #1 (drug overdose) or definition #2 opioid-related mortality) nor does it show significantly lower year-to-year increases in opioid sales after states' initiation of PDMP's.

Thus, a focused difference-of-differences analysis has no impact on our findings.

- Ed Kilbourne.